

### Remarks

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Thus, claim 1 has been amended so that the preamble refers to an ointment external preparation, based on page 8, line 9 of the specification, and also to incorporate the subject matter of claims 3, 4, 8, 11 and 12, as a result of which these dependent claims have been cancelled. Amended claim 1 also expresses, in the last few lines, that the water-soluble polymer in the preparation is in sol state before use, and then the water-soluble polymer simultaneously shows phase transition to gel after the preparation absorbs exudation in a wounded area of the skin, based on, for example, page 6, lines 15-20 and the sentence bridging pages 8-9 of the specification.

Amended claim 1, as well as amended claims 2 and 10, adopt some of the Examiner's suggestions for amending the claims.

New claims 14 and 15 have been added to the application. Claim 14 is supported by page 17, line 19; and claim 15 corresponds to amended claim 1 except that the water-soluble polymer is sodium polyacrylate (page 7, line 17 of the specification), the crosslinking agent is an aluminum-containing crosslinking agent (claim 7), the bactericidal agent is an iodine (page 17, line 19), and the fluidization agent is macrogol (claim 13).

In view of the claim amendments, it is apparent that the objection to claims 8 and 9 on page 2 of the Office Action have been rendered moot.

The rejection of claims 1, 8 and 9 under the first paragraph of 35 U.S.C. §112 should apparently apply only to claim 9, which is the only claim that refers to an iodine-based bactericidal agent. In any case, this rejection has been rendered moot in view of the cancellation of claim 9.

The rejection of claims 1-13 under the second paragraph of 35 U.S.C. §112, based on items 1) to 8) on pages 5-6 of the Office Action has been rendered moot in view of the claim amendments. Thus, the only remaining ground for this rejection is in item 9), which is respectfully traversed.

The Examiner takes the position that claim 13 contains the trademark/trade name "macrogol". However, this term became generic, and is used as the trivial name for polyethylene glycol. For example, "macrogol" is described as another name of polyethylene glycol as well as

PEG in Merck Index (please see the enclosed Reference 1). Further, macrogol is defined as “Mixtures of polymers with the general formula  $H-(OCH_2-CH_2)_n-OH$  where n represents the average number of oxyethylene groups” in EUROPEAN PHARMACOPOEIA 6.0 (please see the enclosed Reference 2). Furthermore, macrogol is cited as an ointment base as well as paraffin and glycerol fatty acid esters in US 5,362,497 (column 6, lines 26-29) cited by the Examiner.

For these reasons, Applicants take the position that the term “macrogol” does not render claim 13 indefinite.

The patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

The rejection of claims 1-7 and 12-13 under 35 U.S.C. §102(b) as being anticipated by Shirai et al. (US ‘105) has been rendered moot in view of the claim amendments. That is, both claims 8 and 11, which are not subject to this rejection, have been incorporated into amended claim 1.

The rejection of claims 1-5, 7 and 11 under 35 U.S.C. §102(b) as being anticipated by Anderson (US ‘562) has been rendered moot. The subject matter of claims 8 and 12, neither of which is subject to this rejection, has been incorporated into amended claim 1.

The rejection of claims 1-4, 12 and 13 under 35 U.S.C. §102(b) as being anticipated by Yamada et al. (US ‘497) has been rendered moot. The subject matter of claims 8 and 11, neither of which is subject to this rejection, has been incorporated into amended claim 1.

The rejection of claims 1-4 and 10 under 35 U.S.C. §102(b) as being anticipated by Makita et al. (US ‘636) has been rendered moot. The subject matter of claims 8, 11 and 12, none of which is subject to this rejection, has been incorporated into amended claim 1.

The rejection of claims 8 and 9 under 35 U.S.C. §103(a) as being unpatentable over Shirai et al. in view of Burks has been rendered moot. The subject matter of claim 11, which is not subject to this rejection, has been incorporated into amended claim 1, on which claims 8 and 9 were directly or indirectly dependent.

The rejection of claim 10 under 35 U.S.C. §103(a) as being unpatentable over Shirai et al. in view of Makita et al. has been rendered moot. The subject matter of claims 8 and 11, neither

of which is subject to this rejection, has been incorporated into amended claim 1, on which claim 10 depends.

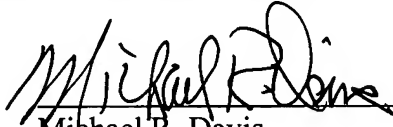
The rejection of claim 11 under 35 U.S.C. §103(a) as being unpatentable over Shirai et al. in view of Anderson has been rendered moot. The subject matter of claim 8, which is not subject to this rejection, has been incorporated into amended claim 1, from which claim 11 depended.

Thus, all of the prior art rejections set forth by the Examiner have been rendered moot in view of the claim amendments.

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of objection and rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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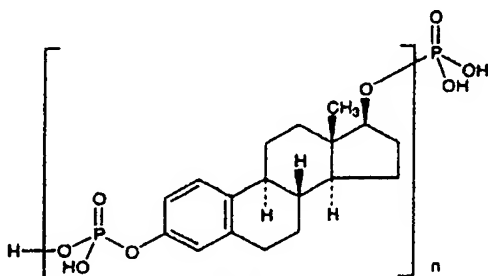
## Polydextrose

titled "Alternative Sweeteners", L. O. Nabors, R. C. Gelardi, Eds. (1991) pp 401-421.

White to light tan, amorphous powder, mp >130°. Bland, non-sweet taste. Hygroscopic. pH of 10% w/w aq soln: 2.5-3.5. Viscosity of 50% aq soln: 35 cps. Very sol in water (to ~80%). Partially sol in glycerin, propylene glycol. Insol in ethanol. Caloric utilization value in humans: 1 kcal/g.

USE: Bulking agent for reduced calorie foods.

**7649. Polyestradiol Phosphate.** [28014-46-2] Estradiol phosphate polymer, PEP: Estradurin. Polymeric ester of phosphoric acid and estradiol. Mol wt ~26,000. Prepn: Diczfalusy, *Endocrinology* 54, 471 (1954); Pernö *et al.*, *Acta Chem. Scand.* 12, 1675 (1958); Diczfalusy *et al.*, *US* 2928849 (1960 to AB Leo). Clinical pharmacology: P. O. Gunnarsson, B. J. Nordén, *Prostate* 13, 299 (1988). Clinical trial in prostatic carcinoma: J. Aro, *ibid.* 18, 131 (1991).

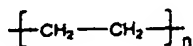


n is approx. 80

Solid, mp 195-202°. Very sol in aq pyridine; sol in aq alkali; very slightly sol in ethanol, ethanol + water (1:1), water, dioxane, acetone, chloroform. Intrinsic viscosity  $[\eta]$  in 0.25M NaCl soln at pH 7.5 = 0.04.

THERAP CAT: Antineoplastic (hormonal).

**7650. Polyethylene.** [9002-88-4] Ethene homopolymer; Agilene; Alathon; Alkathene; Courlene; Lupolen; Platilon; Polythene; Pylon; Reevon. Mol wt about 1500-100,000. C 85.7%, H 14.3%. Prepd by polymerization of liq ethylene at high temps and high or low pressure. Reviews: Aggarwal, *Sweeting, Chem. Rev.* 57, 665-742 (1957); Raff, Allison, *Polyethylene*, vol. XI of High Polymers series (Interscience, New York, 1956); Faith *et al.*, *Industrial Chemicals* (Wiley, New York, 3rd ed., 1965) pp 624-630.



Plastic solid of milky transparency.  $d_4^{20}$  0.92. Tough and flexible at room temps, mp 85-110°. Breaks with cryst fracture at -50°. Good electrical insulator. Surface resistivity:  $10^{14}$  ohms. Will burn, but hardly supports combustion. Stable to water, non-oxidizing acids and alkalis, alcohols, ethers, ketones, esters at ordinary temps. Attacked by oxidizing acids such as nitric acid and perchloric acid, free halogens, benzene, petrol ether, gasoline and lubricating oils, aromatic and chlorinated hydrocarbons.

USE: Laboratory tubing; in making prostheses; electrical insulation; packaging materials; kitchenware; tank and pipe linings; paper coatings; textile stiffeners.

**7651. Polyethylene Glycol.** [25322-68-3]  $\alpha$ -Hydro- $\omega$ -hydroxypoly(oxy-1,2-ethanediyl); macrogol; PEG; Carbowax; Pluracol E; Poly-G; Polyglycol E. Liquid and solid polymers of the general formula  $H(OCH_2CH_2)_nOH$ , where  $n$  is greater than or equal to 4. In general, each PEG is followed by a number which corresponds to its average mol wt. Synthesis: Fordyce, Hibbert, *J. Am. Chem. Soc.* 61, 1905, 1910 (1939). Reviews: Glycols, G. O. Curme, Jr., F. Johnston, Eds., A.C.S. Monograph Series no. 114 (Reinhold, New York, 1952) pp 176-202; Kastens in *High Polymers*, H. Mark *et al.*, Eds., vol. 13 entitled *Poly-*

*ethers*, part 1 (Interscience, New York, 1963) pp 169-189, 274-291; G. M. Powell, III in *Handbook of Water-Soluble Gums & Resins*, R. L. Davidson, Ed. (McGraw-Hill, New York, 1980) pp 18/1-18/31.

Clear, viscous liquids or white solids which dissolve in water forming transparent solns. Sol in many organic solvents. Readily sol in aromatic hydrocarbons. Only slightly sol in aliphatic hydrocarbons. Do not hydrolyze or deteriorate on storage, will not support mold growth. Solvent action on some plastics. Polyethylene glycols are compds of low toxicity: Smyth *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.* 39, 349 (1950). Toxicity data (PEG 400): W. Bartsch *et al.*, *Arzneimittel-Forsch.* 26, 1581 (1976).

**Polyethylene glycol 200.** Average value of  $n$  is 4, mol wt range 190-210. Viscous, hygroscopic liq; slight characteristic odor;  $d_4^{25}$  1.127. Viscosity (210°F): 4.3 centistokes. Supercools upon freezing.

**Polyethylene glycol 400.** Average value of  $n$  between 8.2 and 9.1, mol wt range 380-420. Viscous, slightly hygroscopic liq; slight characteristic odor;  $d_4^{25}$  1.128. mp 4-8°. Viscosity (210°F): 7.3 centistokes. LD<sub>50</sub> orally in rats: 30 ml/kg (Bartsch).

**Polyethylene glycol 600.** Average value of  $n$  between 12.5 and 13.9, mol wt range 570-630. Viscous, slightly hygroscopic liq; characteristic odor;  $d_4^{25}$  1.128. mp 20-25°. Viscosity (210°F): 10.5 centistokes.

**Polyethylene glycol 1500.** Average value of  $n$  between 29 and 36, mol wt range 1300-1600. White, free-flowing powder;  $d_4^{25}$  1.210. mp 44-48°. Viscosity (210°F): 25-32 centistokes.

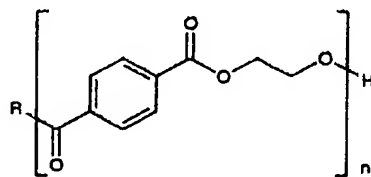
**Polyethylene glycol 4000.** Average value of  $n$  between 68 and 84, mol wt range 3000-3700. White, free-flowing powder or creamy-white flakes;  $d_4^{25}$  1.212. mp 54-58°. Viscosity (210°F): 76-110 centistokes. LD<sub>50</sub> orally in rats (divided doses): 59 g/kg (Smyth).

**Polyethylene glycol 6000.** Average value of  $n$  between 158 and 204, mol wt range 7000-9000. Powder or creamy-white flakes;  $d_4^{25}$  1.21. mp 56-63°. Viscosity (210°F): 470-900 centistokes. LD<sub>50</sub> orally in rats: >50 g/kg (Smyth).

USE: As water-soluble lubricants for rubber molds, textile fibers, and metal-forming operations. In food and food packaging. In hair preps, in cosmetics in general. Pharmaceutical aid (ointment and suppository base). As a stationary phase in gas chromatography. Also in water paints, paper coatings, polishes and in the ceramics industry.

THERAP CAT (VET): Ointment base.

**7652. Polyethylene Terephthalates.** PET. Fiber forming polyesters prepd from terephthalic acid, *q.v.* or its esters and ethylene glycol: Whinfield, Dickson, *US* 2465319 (1949 to du Pont). Review of structures, definition of trade names: R. W. Moncrieff, *Man-Made Fibres* (John Wiley & Sons, New York, 4th ed., 1963) pp 361-389, 707-723.



Dacron R = OH  
Terylene R = OCH<sub>3</sub>

R = OH, *Dacron*, *Amlar*, *Fiber V*. Solid, dec at approx 250°. Sp gr 1.38. Sol in hot *m*-cresol, trifluoroacetic acid, *o*-chlorophenol, a mixture of 7 parts of trichlorophenol and 10 parts (by wt) of phenol, a mixture of 2 parts of tetrachloroethane and 3 parts (by wt) of phenol. Fiber has good resistance to weak acids even at boiling temp, to strong acids in the cold, to weak alkalis, to bleaches, to most alcohols, ketones, soaps, detergents, and dry cleaning agents. Fabric has good resistance to creasing, abrasion, heat aging, and sunlight when behind glass. When "heat-set", fabric will not shrink in either boiling water or boiling drycleaning solvent. Fabric burns, but local melting gen-

01/2008:1125 Saponification value (2.5.6): maximum 3.0.

**MACROGOL OLEYL ETHER****Macrogoli aether oleicus****DEFINITION**

Mixture of ethers of mixed macrogols with linear fatty alcohols, mainly oleyl alcohol. It contains a variable amount of free oleyl alcohol and it may contain free macrogols. The number of moles of ethylene oxide reacted per mole of oleyl alcohol is 2 to 20 (nominal value). A suitable antioxidant may be added.

**CHARACTERS**

- Macrogol oleyl ether with 2 to 5 units of ethylene oxide per molecule.

*Appearance*: yellow liquid.

*Solubility*: practically insoluble in water, soluble in alcohol, practically insoluble in light petroleum.

- Macrogol oleyl ether with 10 to 20 units of ethylene oxide per molecule.

*Appearance*: yellowish-white waxy mass.

*Solubility*: dispersible or soluble in water, soluble in alcohol, practically insoluble in light petroleum.

**IDENTIFICATION**

- It complies with the test for hydroxyl value (see Tests).
- It complies with the test for iodine value (see Tests).
- It complies with the test for saponification value (see Tests).
- Dissolve or disperse 0.1 g in 5 ml of *alcohol R*, add 2 ml of *water R*, 10 ml of *dilute hydrochloric acid R*, 10 ml of *barium chloride solution R1* and 10 ml of a 100 g/l solution of *phosphomolybdic acid R*. A precipitate is formed.

**TESTS**

**Appearance of solution.** The solution is not more intensely coloured than reference solution BY<sub>5</sub> (2.2.2, *Method II*).

Dissolve 5.0 g in *alcohol R* and dilute to 50 ml with the same solvent.

**Alkalinity.** Dissolve 2.0 g in a hot mixture of 10 ml of *water R* and 10 ml of *alcohol R*. Add 0.1 ml of *bromothymol blue solution R1*. Not more than 0.5 ml of 0.1 M *hydrochloric acid* is required to change the colour of the indicator to yellow.

**Acid value (2.5.1):** maximum 1.0, determined on 5.0 g.

**Hydroxyl value (2.5.3, *Method A*).** See Table 1125-1.

**Iodine value (2.5.4).** See Table 1125-1.

Table 1125-1

Ethylene oxide units per molecule (nominal value)	Hydroxyl value	Iodine value
2	158 - 178	48 - 74*
5	110 - 125	48 - 56
10	75 - 95	24 - 38
20	40 - 65	14 - 24

\* This broad range is needed since 2 different grades of oleyl alcohol may be used for the synthesis. The iodine value does not differ by more than 5 units from the nominal iodine value and is within the limits stated in the table.

**Peroxide value (2.5.5):** maximum 10.0.

Saponification value (2.5.6): maximum 3.0.

**Ethylene oxide and dioxan (2.4.25):** maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

**Water (2.5.12):** maximum 3.0 per cent, determined on 2.00 g.

**Total ash (2.4.16):** maximum 0.2 per cent, determined on 2.0 g.

**STORAGE**

In an airtight container, protected from light.

**LABELLING**

The label states:

- the number of moles of ethylene oxide reacted per mole of oleyl alcohol (nominal value),
- the nominal iodine value for the type with 2 units of ethylene oxide per molecule.

01/2008:1444

**MACROGOLS****Macrogola****DEFINITION**

Mixtures of polymers with the general formula  $H-(OCH_2-CH_2)_n-OH$  where  $n$  represents the average number of oxyethylene groups. The type of macrogol is defined by a number that indicates the average relative molecular mass. A suitable stabiliser may be added.

**CHARACTERS**

Type of macrogol	Appearance	Solubility
300	clear, viscous.	miscible with water, very soluble in acetone, in alcohol, and in methylene chloride, practically insoluble in fatty oils and in mineral oils
400	colourless or almost colourless	
600	hygroscopic liquid	
1000	white or almost white, hygroscopic solid with a waxy or paraffin-like appearance	very soluble in water, freely soluble in alcohol and in methylene chloride, practically insoluble in fatty oils and in mineral oils
1500	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, freely soluble in alcohol, practically insoluble in fatty oils and in mineral oils
3000	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, very slightly soluble in alcohol, practically insoluble in fatty oils and in mineral oils
3350		
4000	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, practically insoluble in alcohol and in fatty oils and in mineral oils
6000		
8000		
20 000	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water, soluble in methylene chloride, practically insoluble in alcohol and in fatty oils and in mineral oils
35 000		

**IDENTIFICATION**

- It complies with the test for viscosity (see Tests).
- To 1 g in a test-tube add 0.5 ml of *sulphuric acid R*, close the test-tube with a stopper fitted with a bent delivery tube and heat until white fumes are evolved. Collect the fumes via the delivery tube into 1 ml of *mercuric chloride solution R*. An abundant white, crystalline precipitate is formed.

C. To 0.1 g add 0.1 g of *potassium thiocyanate R* and 0.1 g of *cobalt nitrate R* and mix thoroughly with a glass rod. Add 5 ml of *methylene chloride R* and shake. The liquid phase becomes blue.

### TESTS

**Appearance of solution.** The solution is clear (2.2.1) and not more intensely coloured than reference solution BY<sub>6</sub> (2.2.2, Method II).

Dissolve 12.5 g in *water R* and dilute to 50 ml with the same solvent.

**Acidity or alkalinity.** Dissolve 5.0 g in 50 ml of *carbon dioxide-free water R* and add 0.15 ml of *bromothymol blue solution R1*. The solution is yellow or green. Not more than 0.1 ml of 0.1 M *sodium hydroxide* is required to change the colour of the indicator to blue.

**Viscosity (2.2.9).** The viscosity is calculated using a density given in Table 1444.-1.

Table 1444.-1

Type of macrogol	Kinematic viscosity (mm <sup>2</sup> ·s <sup>-1</sup> )	Dynamic viscosity (mPa·s)	Density* (g/ml)
300	71 - 94	80 - 105	1.120
400	94 - 116	105 - 130	1.120
600	13.9 - 18.5	15 - 20	1.080
1000	20.4 - 27.7	22 - 30	1.080
1500	31 - 46	34 - 50	1.080
3000	69 - 93	75 - 100	1.080
3350	76 - 110	83 - 120	1.080
4000	102 - 158	110 - 170	1.080
6000	185 - 250	200 - 270	1.080
8000	240 - 472	260 - 510	1.080
20 000	2500 - 3200	2700 - 3500	1.080
35 000	10 000 - 13 000	11 000 - 14 000	1.080

\*Density of the substance for macrogols 300 and 400. Density of the 50 per cent *m/m* solution for the other macrogols.

For macrogols having a relative molecular mass greater than 400, determine the viscosity on a 50 per cent *m/m* solution of the substance to be examined.

**Freezing point (2.2.18).** See Table 1444.-2.

Table 1444.-2

Type of macrogol	Freezing point (°C)
600	15 - 25
1000	35 - 40
1500	42 - 48
3000	50 - 56
3350	53 - 57
4000	53 - 59
6000	55 - 61
8000	55 - 62
20 000	minimum 57
35 000	minimum 57

**Hydroxyl value.** Introduce *m* g (see Table 1444.-3) into a dry conical flask fitted with a reflux condenser. Add 25.0 ml of *phthalic anhydride solution R*, swirl to dissolve and boil under a reflux condenser on a hot plate for 60 min. Allow to cool. Rinse the condenser first with 25 ml of *pyridine R* and then with 25 ml of *water R*, add 1.5 ml of *phenolphthalein solution R* and titrate with 1 M *sodium hydroxide* until a faint pink colour is obtained (*n*<sub>1</sub> ml). Carry out a blank test (*n*<sub>2</sub> ml). Calculate the hydroxyl value using the expression:

$$\frac{56.1 \times (n_2 - n_1)}{m}$$

Table 1444.-3

Type of macrogol	Hydroxyl value	<i>m</i> (g)
300	340 - 394	1.5
400	264 - 300	1.9
600	178 - 197	3.5
1000	107 - 118	5.0
1500	70 - 80	7.0
3000	34 - 42	12.0
3350	30 - 38	12.0
4000	25 - 32	14.0
6000	16 - 22	18.0
8000	12 - 16	24.0
20 000	-	-
35 000	-	-

For macrogols having a relative molecular mass greater than 1000, if the water content is more than 0.5 per cent, dry a sample of suitable mass at 100-105 °C for 2 h and carry out the determination of the hydroxyl value on the dried sample.

**Reducing substances.** Dissolve 1 g in 1 ml of a 10 g/l solution of *resorcinol R* and warm gently if necessary. Add 2 ml of *hydrochloric acid R*. After 5 min the solution is not more intensely coloured than reference solution R<sub>3</sub> (2.2.2, Method I).

**Formaldehyde:** maximum 30 ppm.

**Test solution.** To 1.00 g add 0.25 ml of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 ml of *sulphuric acid R*. Allow to stand for 15 min and complete slowly to 10 ml with *water R*.

**Reference solution.** Dilute 0.860 g of *formaldehyde solution R* to 100 ml with *water R*. Dilute 1.0 ml of this solution to 100 ml with *water R*. In a 10 ml flask, mix 1.00 ml of this solution with 0.25 ml of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 ml of *sulphuric acid R*. Allow to stand for 15 min and complete slowly to 10 ml with *water R*.

**Blank solution.** In a 10 ml flask mix 1.00 ml of *water R* with 0.25 ml of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 ml of *sulphuric acid R*. Complete slowly to 10 ml with *water R*.

Determine the absorbance (2.2.25) of the test solution at 567 nm, against the blank solution. It is not higher than that of the reference solution.

If the use of macrogols with a higher content of formaldehyde may have adverse effects, the competent authority may impose a limit of not more than 15 ppm.